IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicant(s): Gleave, et al. Application No.: 09/913,325 Filed: 8/10/2001 Title: TRPM-2 Antisense Therapy Attorney Docket No.: UBC.P-020 Customer No.: 57381	Group Art Unit: 1635 Examiner: Tracy Vivlemore Confirmation No: 8469

DECLARATION UNDER RULE 132

I, Martin Gleave, declare as follows:

1. I am a named inventor of the above-captioned application, and as such am familiar with the application including the claims. I am also a co-author of the Bruchovsky et al., Prostate Suppl. 6: 13-21 (1996) paper ("Bruchovsky et al."), which has been cited by the Examiner in an Official Action for this application.

2. In the Official Action, the Examiner states that "on page 20 Bruchovsky et al. suggest a prostate cancer treatment that includes augmentation of intermittent therapy by administration of additional chemotherapeutic agents. Bruchovsky et al. explicitly suggest anti-TRPM-2 or anti-Bcl-2 gene therapy in conjugation with androgen withdrawal/replacement."

3. The passage to which the Examiner refers is in a section of the paper entitled "Future Directions." At the time Bruchovsky et al. was written, we, as the authors of the paper, intended this as an indication of the direction that our research would take, and not as a statement that anti-TRPM-2 would necessarily provide a therapeutic benefit. Further, as a researcher studying this area, I would not understand this passage to provide an expectation of any particular result from the proposed experiments once performed. At

that time, it simply was not known whether a decrease in TRPM-2 levels would cause or prevent apoptosis.

4. The inability to predict the outcome of the experiments indicated as "future directions" persisted until the time of the experiments that are the basis of the presently claimed invention. As noted in the specification of this application, the results of testing concerning the role of TRPM-2 were ambiguous and did not clearly define a role for this protein.

5. For example, in Sensibar et al. cited by the Examiner, the statement is made that the prior observations in the literature "have left the possibility of [TRPM-2] being associated with prostatic cell death questionable; much less certain is the role of [TRPM-2] in cell death." (page 2431, Col. 2). Although it was not known at that time, there are different isoforms of clusterin with different functions, and this fact contributed to the ambiguity in findings prevalent at that time. Briefly, a nuclear form of CLU protein (nCLU) promotes apoptosis, and a secretory form (sCLU), promotes survival. Enclosed is one paper by Shannan, B. et al. (2006), which discusses the different isoforms and the difficulties posed thereby.

6. Based on the state of the art at the time the invention was filed, I as an inventor and a person skilled in the art believe that the outcome of the proposed experiment of combining antisense therapy targeted to TRPM-2 and cyclic androgen withdrawal could not have reasonably been predicted.

7. In addition, nothing in the art would have predicted the synergistic effect of combinations of antisense therapy targeted to TRPM-2 and chemotherapy agents. Attached are two graphs. These graphs reflect data from the same set of experiments, but the scale on the Y-axes is so different that two graphs are needed to accurately depict the results. In the experiment, we observed the effects of antisense therapy targeted to TRPM-2 on PC-3 prostate tumor growth. When PC-3 tumors became ~1 cm in diamteter, 10mg/kg of

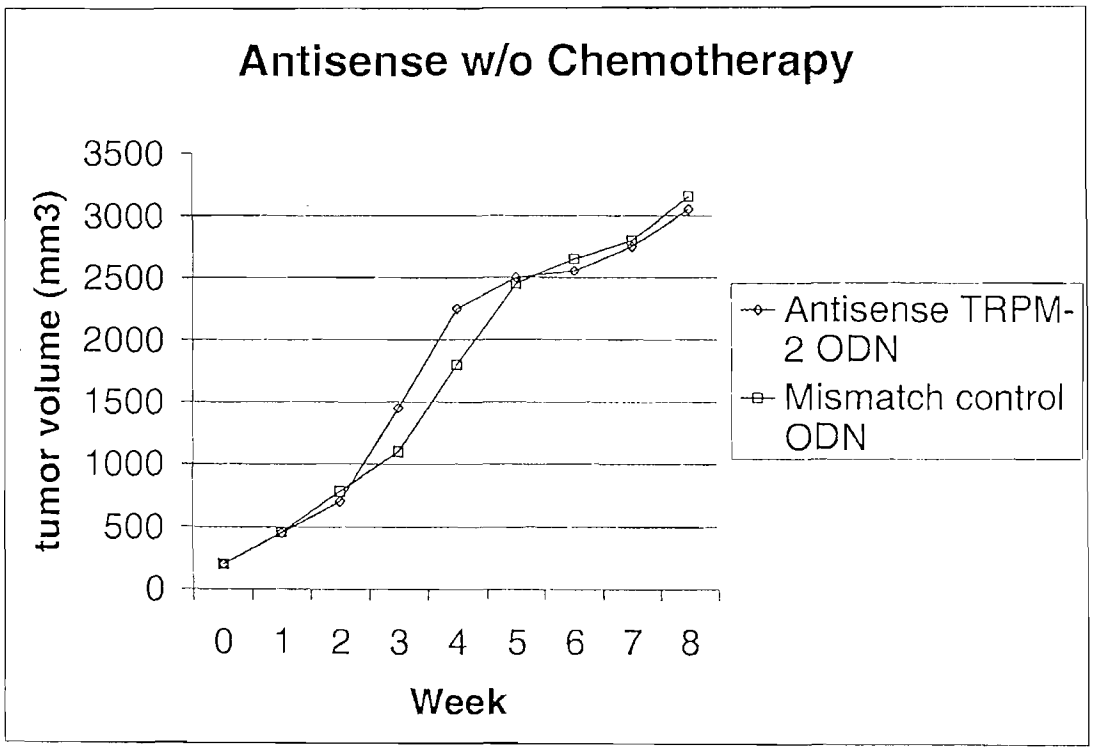
antisense CAGCAGCAGAGTCTTCATCAT or 2 base mismatch (MM) control were injected I.p. once daily for 28 days into each mouse. Tumor volume was measured once weekly and calculated by the formula: Length x width x depth x 0.5236. Each data point represents the average of 8 mice.

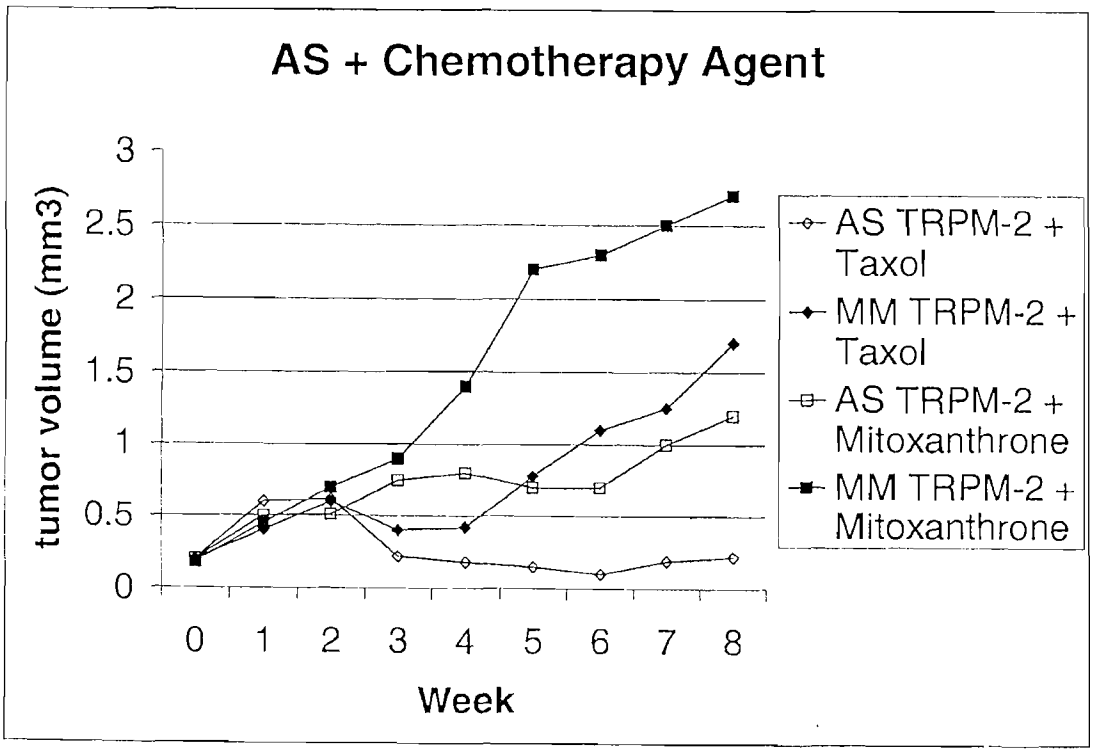
8. As can be seen in the first figure, there was essentially no difference in tumor volume between mice treated with antisense alone or the mismatch control. The second figure, on which the scale of the Y-axis is smaller, shows that treatment with a chemotherapy agent and the mismatch control oligonucleotide resulted in much smaller tumors (solid symbols). Even better results were obtained using the antisense in combination with the chemotherapy agent (open symbols), notwithstanding the fact that the antisense alone did not improve the performance relative to the mismatch control alone.

I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of the application or any patent issued thereon.

Aug 30 / 06
dated

Martin Gleave


Antisense w/o Chemotherapy
tumor volume (mm3)
3500
3000
2500
2000
1500
1000
500
0
0 1 2 3 4 5 6 7 8
Week
Antisense TRPM-2 ODN
Mismatch control ODN


AS + Chemotherapy Agent
tumor volume (mm3)
3
2.5
2
1.5
1
0.5
0
0 1 2 3 4 5 6 7 8
Week
AS TRPM-2 + Taxol
MM TRPM-2 + Taxol
AS TRPM-2 + Mitoxanthrone
MM TRPM-2 + Mitoxanthrone